US 20030059397A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0059397 A1**

Hughes (43) **Pub. Date: Mar. 27, 2003**

(54) **DOSAGE FORMS**

(76) Inventor: **Lyn Hughes**, Harleysville, PA (US)

Correspondence Address:
ROHM AND HAAS COMPANY
PATENT DEPARTMENT
100 INDEPENDENCE MALL WEST
PHILADELPHIA, PA 19106-2399 (US)

(21) Appl. No.: **10/016,415**

(22) Filed: **Nov. 2, 2001**

Related U.S. Application Data

(60) Provisional application No. 60/322,768, filed on Sep. 17, 2001.

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/74**

(52) **U.S. Cl.** **424/78.1**

(57) **ABSTRACT**

Solid oral dosage forms of controlled substances are described that have reduced potential for abuse by inhalation, mastication, and injection.

DOSAGE FORMS

[0001] This application claims benefit to provisional application No. 60/322,768, filed Sep. 17, 2001.

BACKGROUND

[0002] Abuse of controlled substances is a serious and growing problem throughout the world. For example, the abuse of an extended release form of oxycodone has been the recent subject of many articles such as 'Playing With Pain Killers' and 'How One Town Got Hooked'. See, Newsweek, Apr. 9, 2001, pages 45-51. Further, The New York Times profiled the problem of oxycodone abuse by inhalation of the crushed pill. See, The New York Times, Jul. 29, 2001. It is estimated that in America four million people over the age of 12 used prescription painkillers and stimulants for non-medical reasons in the space of just one month, approximately half of them saying they'd done it for the first time. Emergency room visits related to such abuse approximately doubled between 1992 and 1999.

[0003] There are three main routes that drug abusers use for administering the drug substances: parenteral, oral, and inhalation. The parenteral route is commonly called 'mainlining' and requires the drug substance to be in solution such that it can be injected intravenously with a syringe. For solid dosage form drugs this requires some type of extraction and concentration procedure to render the drug substance suitable for injection. Inhalation of a solid drug substance through the nose is commonly called 'snorting'. For solid dosage form drugs this requires only that the dosage form be crushed into a powder, or emptied from a capsule. Breathing in vapors is frequently known as 'huffing'. Both snorting and huffing result in the rapid absorption of the drug substance through the mucosa of the respiratory system.

[0004] The potential for abuse is increased by the use of extended release formulations because they typically contain more than the immediate release single dose of active ingredient. Circumventing the extended release mechanism delivers the full dose, which is intended to be delivered over a longer time period, immediately. For example, crushing an extended release oxycodone tablet separates a gelling matrix from the oxycodone active ingredient, such that when inhaled through the nose the gelling matrix cannot exert the extended release effect. Similarly it is sometimes possible to circumvent the extended release effect by chewing the dosage form.

[0005] The use of coatings to extend the release of drug substances is very well known in the art. See, Remington's Pharmaceutical Sciences, 16th Edition, Chapter 90. Such dosage forms are also subject to said modes of abuse because the coating can be damaged by crushing or chewing.

[0006] WO0108661 describes an extended release dosage form of opioids that uses an ion exchange resin. This dosage form is also subject to said modes of abuse because the ion exchange resin and the active ingredient can be separated by crushing.

[0007] Various methods have been used to reduce the potential for abuse of controlled substances. These methods have focused on the parenteral and oral routes of administration.

[0008] U.S. Pat. Nos. 3,773,955, 3,966,940, and 4,457,933 describe oral dosage forms containing a combination of opioid agonists and antagonists, in which the effect of the antagonist when administered according to the correct procedure does not affect the therapeutic pain management value of the agonist. However, when the agonist and antagonist are extracted for parenteral administration by an addict the effect of the agonist desired by the addict is decreased. This approach was further adopted in WO9004965 where it was incorporated into a transdermal delivery device, and in U.S. Pat. No. 6,228,863 where it was developed into a dosage form from which the agonist could not be separated from the antagonist except by using a sophisticated multi-step procedure.

[0009] In U.S. Pat. No. 3,980,766 multiple methods for reducing abuse potential are described. One method is to include a thickening agent such that the concentrated extract containing the drug can not be injected with a syringe. Another is the incorporation of agents that cause the precipitation of the drug during isolation, thus rendering it unsuitable for injection. The addition of a thickener has also been used in U.S. Pat. No. 4,070,494, WO9107950, and WO9520947.

[0010] In WO0033835 additives are included in the dosage forms such that when added to drinks create a visible change in the drink. This invention reduces the potential for abuse by oral administration of the substance by one person to another without their knowledge.

[0011] However, none of the cited references solve the problem of potential abuse via inhalation or mastication of an oral dosage form. Applicants have surprisingly discovered an oral dosage form useful in reducing the potential for drug abuse via inhalation, mastication, or injection of illicit extracts of said oral dosage form.

[0012] The term "therapeutic concentration" as used herein means the concentration of the pharmaceutically active ingredient in the blood plasma that is obtained by the administration of the recommended doses using the prescribed method of administration. Recommended doses for Schedule II-V controlled substances are defined in the literature. For example, see 'Drug Facts and Comparisons', published by Facts and Comparisons, St Louis.

[0013] The term "high," as used herein means the non-therapeutic effect desired by drug addicts and recreational drug users The term "mucosal membrane" as used herein means any mucosal membrane of the body through which an active substance can be administered, including, but not limited to, nasal, lingual, buccal, pharyngeal, bronchial, rectal, urethral and vaginal.

[0014] The term "respiratory mucosal membrane" as used herein means the mucous membrane lining the nasal and pharyngeal cavities, the bronchial tubes, and the lungs. Typically, snorting into the nasal cavity is the common, preferred route of abuse for a solid oral dosage form which has been crushed by one intending to inhale said crushed dosage form to obtain the high.

[0015] The term "illicit extracts" as used herein are those extracts obtained by any of the means known to drug addicts, drug users, and recreational drug users for extracting an active substance from an oral dosage form. In the interests of social responsibility these methods will not be described herein.

[0016] The term "sensory agent" as used herein means those agents that modify ones sensory perception of the dosage form.

[0017] The term "meq/g", as used herein, refers to the fact that ion exchange resins are characterized by their capacity to exchange ions. This is expressed as the "Ion Exchange Capacity." For cation exchange resins the term used is "Cation Exchange Capacity," and for anion exchange resins the term used is "Anion Exchange Capacity." The ion exchange capacity is measured as the number equivalents of an ion that can be exchanged and can be expressed with reference to the mass of the polymer (herein abbreviated to "Weight Capacity") or its volume (often abbreviated to "Volume Capacity"). A frequently used unit for weight capacity is "milliequivalents of exchange capacity per gram of dry polymer." This is commonly abbreviated to "meq/g."

SUMMARY OF THE INVENTION

[0018] The present invention relates to an oral pharmaceutical dosage form not susceptible to abuse by mucosal membrane administration providing a plasma concentration that does not exceed the therapeutic concentration.

[0019] The present invention also relates to an oral pharmaceutical dosage form not susceptible to abuse by respiratory mucosal membrane administration providing a plasma concentration that does not exceed the therapeutic concentration.

[0020] The present invention further relates to an oral pharmaceutical dosage form not susceptible to abuse by mastication providing a plasma concentration that does not exceed the therapeutic concentration.

[0021] Finally, the present invention relates to an oral pharmaceutical dosage form not susceptible to abuse by injection of an illicit extract of said oral dosage form providing a plasma concentration that does not exceed the therapeutic concentration.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The present invention relates to an oral pharmaceutical dosage form not susceptible to abuse by mucosal membrane administration providing a plasma concentration that does not exceed the therapeutic concentration.

[0023] The present invention also relates to an oral pharmaceutical dosage form not susceptible to abuse by respiratory mucosal membrane administration providing a plasma concentration that does not exceed the therapeutic concentration.

[0024] The present invention further relates to an oral pharmaceutical dosage form not susceptible to abuse by mastication providing a plasma concentration that does not exceed the therapeutic concentration.

[0025] Finally, the present invention relates to an oral pharmaceutical dosage form not susceptible to abuse by injection of an illicit extract of said oral dosage form providing a plasma concentration that does not exceed the therapeutic concentration. Specifically, the dosage form of the present invention renders the controlled substance unable to deliver the desired non therapeutic effect, i.e., the high.

[0026] The utility of the invention lies in the fact that the rate of release of the controlled substance is not affected by crushing the solid oral dosage form, or of emptying the dosage from a capsule. For example, when said solid oral dosage form is crushed and inhaled, chewed or illicitly extracted and injected for non-therapeutic purposes the controlled substance is not available for total release, but will release at a rate that does not result in a plasma concentration that exceeds the therapeutic concentration. The high is not obtained at the therapeutic concentration.

[0027] The Controlled Substances Act of 1970 regulates the manufacturing, distribution, and dispensing of drugs that have abuse potential. The Drug Enforcement Agency (DEA) within the US Department of Justice is the chief agency responsible for enforcing said act. Drugs under the jurisdiction of said Act are divided into five schedules (I thru V) based on their medical utility, potential for abuse, and physical and psychological dependence. Schedule I substances have high abuse potential and no accepted medical use. Schedule II also have high abuse potential, but also have medical utility. Schedules III, IV, and V have progressively lower abuse potential.

[0028] Because the DEA rates abuse potential based on specific dosage forms it is not uncommon for a drug to be rated in multiple schedules. For example codeine appears as Schedule II, Schedule III, and Schedule IV, depending on the specific dosage form and dosage amount. To avoid duplication in the list of controlled substance below, multiple occurrences have been removed and any controlled substance that had multiple occurrences is placed in the highest abuse potential category for which is has been scheduled. For example, codeine has been included as Schedule II, but not Schedule III or Schedule IV. This is not intended to limit the scope of the invention. The utility of the Applicant's invention lies in the fact that any ionizable controlled substance, regardless of what schedule it appears on, is suitable for formulating into the Applicant's dosage form.

[0029] Controlled substances useful in the practice of the invention are those categorized by the DEA as Schedule II, III, IV, and V controlled substances. Controlled substances useful in the practice of the invention must be ionizable such that a controlled substance-ion exchange resin complex can be formed. Schedule II substances include, but are not limited to, 1-Phenylcyclohexylamine, 1-Piperidinocyclohexanecarbonitrile, Alfentanil, Alphaprodine, Amobarbital, Amphetamine, Anileridine, Benzoylecgonine, Bezitramide, Carfentanil, Cocaine, Codeine, Dextropropoxyphen, Dihydrocodeine, Diphenoxylate, Diprenorphine, Ecgonine, Ethylmorphine, Etorphine HCl, Fentanyl, Glutethimide, Hydrocodone, Hydromorphone, Isomethadone, Levo-alphacetylmethadol, Levomethorphan, Levorphanol, Meperidine, Metazocine, Methadone, Methamphetamine, Methylphenidate, Metopon, Morphine, Nabilone, Oxycodone, Oxymorphone, Pentobarbital, Phenazocine, Phencyclidine, Phenmetrazine, Piminodine, Racemethorphan, Racemorphan, Remifentanil, Secobarbital, Sufentanil, Thebaine Schedule III substances include, but are not limited to, Aprobarbital, Barbituric acid derivative, Benzphetamine, Butabarbital, Butalbital, Chlorphentermine, Ketamine, Lysergic acid, Lysergic acid amide, Nalorphine, Phendimetrazine, Talbutal, Thiamylal, Thiopental, Vinbarbital.